

Seventy-five Years Ago: Insulin Treatment in Hereford General Hospital

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This year, 1998, marks the 75th anniversary of the general availability of insulin in the United Kingdom. To mark the occasion, *Diabetic Medicine* publishes this account of the early days of insulin therapy in one of Britain's district general hospitals, Hereford General Hospital. The authors describe the first tentative use of insulin and draw some interesting parallels with the issues which still concern the introduction of novel therapies in endocrinology today. © 1998 John Wiley & Sons Ltd.

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Introduction

When limited supplies of insulin became available in the UK in February 1923, its use was initially supervised by the Medical Research Council (MRC) in seven designated hospitals.¹ It was not until 12 April 1923 that insulin became commercially available, and at this time the manufacturers were directed to supply only those hospitals and registered medical practitioners who had facilities for measuring blood sugar concentrations. Insulin was not to be given to those patients whose symptoms could be controlled by 'moderate restrictions of diet', and there was to be 'no luxury use of insulin till supplies are abundant'.² On 28 April the results of the early clinical experience in the seven hospitals which had taken part in the MRC study were published.³ The importance of repeated estimations of the blood sugar concentration was again emphasized in an accompanying editorial.⁴ All restrictions on the sale of insulin were finally removed on 26 May, with a further reminder of the importance of measuring the blood sugar concentration.⁵

Insulin Treatment in Hereford

Case 1

On 26 June, one month after removal of the restrictions on the sale of insulin, the House Committee of the Hereford General Hospital (HGH) was asked by Dr Symonds, one of the physicians, to purchase apparatus for measuring blood sugar concentrations in a diabetic patient who was currently in the ward.⁶ However,

another of the physicians, Dr Patterson, 'felt that insulin was not yet proven', and the Committee suggested that the patient be transferred to a hospital which had the equipment. The London Hospital, which had been one of the original seven hospitals in the MRC study, was approached but refused to accept the case. The patient was a 60-year-old railway engine driver who had been admitted on 20 June.⁷ He had been on dietary treatment since the onset of diabetes 3 years earlier when he had presented with a 'great thirst and passage of large quantities of pale urine'. He had originally weighed 10 st 3 lb (65 kg), but was only 6 st 3 lb (39.5 kg) on admission. He was described as 'emaciated and pale', and 'anxious to have insulin'. He had bilateral immature cataracts and the fundi could not be seen. For 5 weeks after admission he was treated only by diet (details illegible except 'no sugar or puddings'), presumably while negotiations were continuing over whether he was to be treated with insulin and, if so, where. On 24 July a report was received on a blood sample which had been sent to the Clinical Research Association in London and which showed a sugar concentration of 0.321 % (17.8 mmol l⁻¹). On 28 July insulin treatment was started in Hereford with 10 units b.d. on a diet which initially consisted of only 'custard and green vegetables'. Treatment was stopped after 1 week, restarted 1 week later with 20–40 units o.d., and continued, usually with a dose of 20 units o.d., on 18 of the next 23 days. During the final 20 days of the admission he received no insulin and was discharged, at his own request, on 22 September. His urine volume, specific gravity and sugar content were measured daily during the admission and the results are summarized in Table 1. After the first week on insulin therapy his weight had increased by 9 lb (4.1 g) to 6 st 12 lb (43.6 kg) but was not recorded again. No further clinical notes have been found. He died on 28 December

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Table 1. Case 1: average urine volume, specific gravity, and sugar content

Date	Treatment	Fluid oz (l) 24 h ⁻¹	Specific gravity	Sugar gm 100 ml ⁻¹ (mmol l ⁻¹)
21.06– 27.07.23	Diet only	76 (2.25)	1032	5.6 (311)
28.07– 03.08.23	Insulin 10 units b.d.	60 (1.78)	1038	6.1 (339)
04.08– 09.08.23	Diet only	75 (2.20)	1031	4.7 (261)
10.08– 01.09.23	Insulin 20 units o.d. except 40 units o.d. on 5 days and none on 5 days	67 (1.98)	1026	2.8 (156)
02.09– 21.09.23	Diet only	57 (1.69)	1022	2.0 (111)

1923, and the cause of death was given as '(1) Glycosuria, (2) Morbus cordis'.⁸

Case 2

During July Dr Patterson, who had told the House Committee in late June that insulin was 'not yet proven', had apparently changed his mind, because on 2 August he admitted a patient with a view to starting him on insulin. The patient was a 59-year-old printer⁹ who had been previously admitted in July 1922 for dietary treatment. When he was re-admitted in August 1923, the hospital had still not purchased equipment for measuring blood sugar concentrations because the sample was sent to Bristol for analysis (Figure 1). Despite the rather modest degree of hyperglycaemia, his age, and the absence of any tests for acetone, it is likely that he had Type 1 diabetes, because he was described as 'emaciated' and weighed only 6 st 13 lb (44 kg). His initial treatment was with a 'restricted diet' with 'no starch' but there was no clinical improvement after 2 weeks, and his case was discussed by the House Committee on 14 August when it was agreed that he be given a 1 month trial of insulin.⁶ The minutes record that the 'Committee were reluctant because of the cost of offering insulin treatment too easily at this experimental stage'. Insulin was started on 18 August with a single daily injection, initially 20–40 units daily, subsequently reduced to 20 units daily and then to 10 units daily. No further analyses were made of blood sugar concentrations, but urine volume, specific gravity and sugar concentrations were measured daily and decreased on insulin therapy (Table 2). No information is given about any change in diet after starting insulin, and it was probably still very restricted as there had been no weight gain by the time of discharge 2 weeks after starting insulin. Outpatient notes have not survived and no subsequent

medical details are available. He died at home on 29 November 1925 and 'Diabetes' was given as the cause of death on the death certificate.¹⁰

Case 3

This patient,¹¹ a 42-year-old man who weighed 7 st 6 lb (47.3 kg), was admitted on 20 September under the care of a consultant surgeon. For the first 6 days he was given 'diet as ordered', but no details of the diet are given in the notes. After starting insulin he was given single daily injections of 5–10 units on 24 of the subsequent 33 days. By the time of discharge, on 10 units of insulin once daily, the average specific gravity of the urine had dropped from 1934 to 1016 and the average sugar content from 4 % to 0.5 %. The discharge notes read 'Much improved—has gained 2 st (12.7 kg) in weight—given Ladder diet—with insulin'. He was readmitted in November 1924, still under the care of a surgeon rather than a physician, when it was noted that he had been receiving insulin 'every 2nd morning'. The dose was increased on admission to 20 units every morning, and then to 10 units three times daily, at 5.45 am, 11.30 am and 3.30 pm which presumably relates to the timing of hospital meals. No further clinical records of this patient have been found. He died at home on 30 September 1930, and the death certificate gave the cause of death as 'Diabetes'.¹²

Case 4

This 24-year-old farmer¹³ was admitted on 18 October 1923 with a history of polydipsia—10–12 pt (5.5–6.5 l) of fluid daily—and was so weak that he was no longer able to work. He had lost 3 st 7 lb (22 kg) in weight and was only 7 st 3 lb (46 kg). His sugar concentration (on a sample which still had to be sent to Bristol for analysis) was 0.231 % (12.8 mmol l⁻¹). He was put on a restricted diet: 'no sugar – no potatoes – no white bread', though some dry toast was subsequently allowed. When he did not improve after 2 weeks, insulin was started, initially 10 units b.d. and subsequently 20 units o.d., and then 30 units o.d. Subsequent notes record that he was gaining weight and feeling well, though he still had 2½ – 3 % glycosuria and occasional acetonuria prior to discharge on a 'restricted diet' on 12 December. No further clinical records have been found, and no death certificate has been traced.

The clinical records for 1924 are incomplete, and it is not known how many patients were admitted for initiation of insulin therapy in that year, but the House Committee was still concerned about the expense because on 23 December 1924 the minutes record 'MOH (Medical Officer of Health) to be quizzed about the possibility of obtaining free supplies of insulin for patients in hospital'.⁶

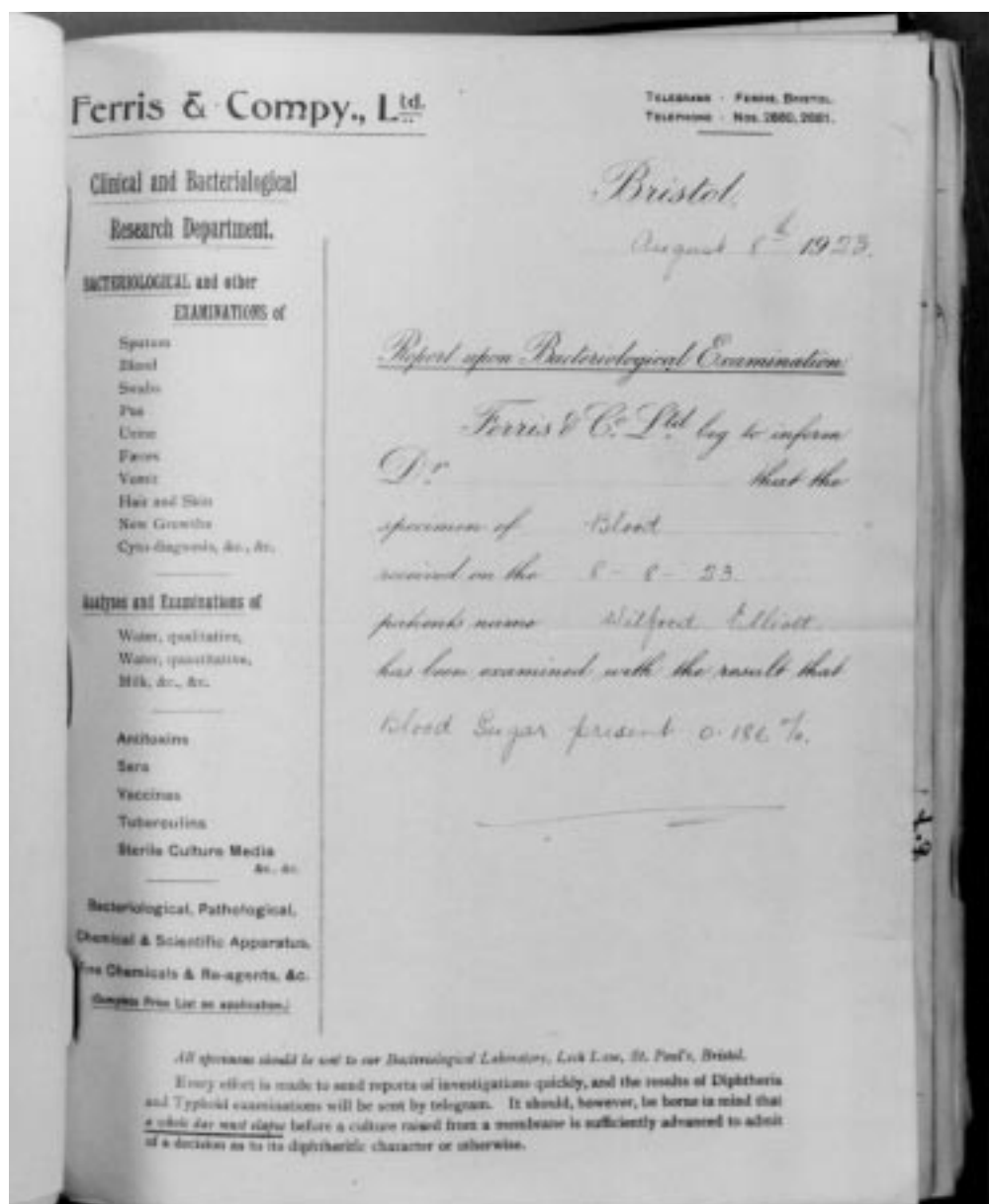


Figure 1. The report of the blood sugar concentration in Case 2

Table 2. Case 2: average urine volume, specific gravity, and sugar content

Date	Treatment	Fluid oz (l) 24 h ⁻¹	Specific gravity	Sugar g 100 ml ⁻¹ (mmol l ⁻¹)
07.08– 16.08.23	Diet only	67 (1.98)	1024	2.7 (150)
24.08– 01.09.23	Insulin 10–20 units o.d.	50 (1.48)	1018	1.0 (56)

Discussion

The 'Experimental' Phase of Insulin Treatment

By mid-September 1923 there were 20 000–25 000 American patients on treatment with insulin,¹⁴ so at first

sight it seems extraordinary that in mid-August the House Committee of the HGH should still be describing insulin treatment as 'experimental', and that, at the end of June, Dr Patterson had described insulin as 'not yet proven', although it was by then on unrestricted sale. However, such opinions were not limited to the staff of a small and isolated provincial hospital. In May 1923 Dr Cammidge, a London physician specializing in diabetes and author of a book on the disease,¹⁵ had written that insulin was invaluable for 'tiding patients over crises. . . or for ensuring a maintenance diet in severe cases where the power to metabolise carbohydrate is permanently lost. . . but for the average patient treatment with insulin, under present conditions is a will-o'-the-wisp, reliance upon which usually ends in disappointment'.¹⁶ As late as August an editorial in the *British Medical Journal* stated that: 'As to the exact value of insulin in the everyday treatment of diabetes, it is yet too soon to

speak', and quoted Professor Macleod to the effect that insulin be regarded 'as an adjunct to therapeutic control'.¹⁷ The House Committee of the HGH could therefore claim some justification for describing insulin therapy as 'experimental', even though its reservations about the use of insulin were probably mainly based on financial grounds.

The Clinical Management of Insulin Therapy in 1923

By the time insulin was used in Hereford the *British Medical Journal* and the *Lancet* had published six papers and letters describing the principles which should govern the initiation of insulin,^{3,18–22} and another seven such papers had appeared by the end of November.^{15,23–28} All of these articles would have been readily available to the Hereford doctors, so how far did they follow the advice which they gave? Although the advice was sometimes rather variable there were at least four areas in which it was generally consistent:

1. *Selection of appropriate patients.* Virtually all the papers emphasized the advice in the MRC report³ that patients should only be given insulin if they failed to respond to a restricted diet, with or without some periods of starvation, and this principle appears to have been followed in all four of the Hereford patients who were initially treated by diet alone after admission, although even in 1923 it must have been obvious from the outset that Case 4 would need insulin.
2. *Administration in relation to food.* Five of the papers mentioned that insulin should be given before food to minimize the risk of hypoglycaemia, with the time interval varying between 20 to 30 minutes¹⁹ and 60 minutes.¹⁵ In the Hereford cases insulin was usually given once daily in 1923, but the timing is not specifically mentioned. When Case 3 was switched to three daily injections in November 1924 the timing was probably related to each of the three main meals.
3. *Insulin dosage.* There was a general consensus that a typical daily dose was 20–40 units, but that the dose must be suited to the individual and it could be as little as 10 or as much as 60 units daily.^{3,15,19,24} It was usually given in two, or occasionally three, equally divided doses, though sometimes just once daily.^{20,23} Only one of the advocates of twice daily injections gave two-thirds of the dose in the morning and one-third in the evening,²¹ the others giving two equal sized doses. A typical starting dose was just 5 units b.d. if blood sugar analysis was not available.²⁸ The Hereford doctors were therefore using orthodox doses, but were among a minority group in using just one daily injection. So far as can be determined from the patients' records they followed standard practice in keeping the diet constant, using moderate

energy restriction and considerable carbohydrate restriction, while adjusting the insulin dosage to match the diet. None of the early British papers made any mention of adjusting either the insulin dosage or dietary intake to compensate for variations in physical activity, but physicians in Ontario advised patients to avoid excessive exercise or heavy work.²⁹ Insulin treatment in all four of the Hereford patients was interrupted for periods ranging from 2 to 7 days. Whether such interruptions were clinical decisions or due to non-availability of insulin is not clear from the notes. The first interruption in Case 1 must have been a clinical decision, because at the time he had received a total of 140 units and, as insulin was supplied in bottles of 100 units,³⁰ there should have been nearly 60 units still in stock. Between 19 and 24 August treatment was interrupted in both patients 1 and 2 which might imply that supplies had run out. The minutes of the House Committee on 2 October record that the 'House Surgeon [is] to obtain sanction before ordering any more insulin', and that the 'general treatment of diabetes with insulin [was] to be referred to the Liaison Committee'.⁶ Both of these decisions might have interrupted the treatment of the third patient. Moreover, according to Bliss,¹⁴ Britain was facing 'an insulin famine' in September 1923 and had to order emergency supplies from America. This may explain why insulin was discontinued during the last 19 days of the admission in Case 1, but is also possible that the doctors regarded the partial 'honeymoon' which had been induced (see Table 1) as constituting acceptable glycaemic control.

4. *Blood sugar measurements.* One of the initial conditions set by the MRC for the supply of insulin was the availability of 'proper facilities... for making blood sugar determinations'.² The need for repeated testing was emphasized in a leading article in the *British Medical Journal*,⁴ and in the clinical report of the MRC study³ though the latter also recognized the problems of repeated testing, and suggested that if it could not be done sufficiently often then the insulin dose should be reduced 'to such a level as will just allow the patients a slight glycosuria as a safety gauge', and this policy was echoed by Maclean.¹⁹ However, the emphasis on blood sugar analyses changed considerably over the next 4 months, so that by mid-September Dr Graham told the Annual General Meeting of the British Medical Association that they were 'of assistance, but not absolutely necessary',¹⁵ and this opinion was subsequently corroborated by other leading British diabetologists.^{24,26,28} In measuring the blood sugar concentration only on admission (presumably to exclude glycosuria of renal origin), but not after initiation of insulin treatment, the Hereford doctors were therefore following what had come to be acceptable practice by the second half of 1923. The lack of facilities for measuring blood sugar levels in

the hospital, and the delay involved in sending samples to London and Bristol, would have made regular monitoring impracticable. It is, however, surprising that the House Committee had still not invested in equipment by the time the fourth patient started insulin in November because, according to the prices quoted by Tattersall,³¹ each analysis in Bristol would probably have cost about 30s 0d (£1.50), whereas the equipment could be purchased for £3 15s 0d (£3.75).

The Cost and Affordability of Insulin

The cost of a typical daily dose of about 30 units of insulin in the second half of 1923 was approximately £2.00 per week³⁰ which represented 22 % of the entire weekly budget of the pharmacy in the HGH; by comparison a week's treatment with human growth hormone in 1997 was only 1.1 % of the budget (Table 3). It is not surprising that the House Committee were concerned by such expenditure. Other hospitals faced the same problem; for example, in Nottingham a week's supply of insulin amounted to 64 % of the average weekly cost of an inpatient.³¹ The HGH was dependent on its investments and charitable donations and subscriptions, and on selling its services, for its income; and, if income from investments is excluded, it was like most other 'voluntary' hospitals, running at a deficit in the 1920s. In 1923 the expenditure of voluntary hospitals in England, Wales and Scotland exceeded income by £737 454,³⁵ and trustees must have regarded the advent of an expensive new treatment with considerable apprehension. Even though the price of insulin had fallen to 6s 8d (£0.33)³¹ per 100 units by April 1924, the House Committee must still have been concerned about the cost when they explored the possibility of getting the local Medical Officer of Health to pay for supplies for inpatients in December of that year. Seventy-five years later it seems ironic that now the boot is on the other

foot, and many general practitioners expect the hospital pharmacies to meet the cost of expensive drugs for outpatients.

For many patients insulin was unaffordable. Expenditure of £100 per annum on insulin was beyond the means of all but the rich, at a time when the average annual income of a guard on a passenger train was £125 and that of a police sergeant was £200.³⁶ In Ontario insulin was provided free for outpatients,²⁰ and in Ireland a public appeal was started to provide an 'Insulin Fund',³⁷ but there were no such provisions elsewhere in the United Kingdom. An editorial in the *Lancet* deplored the fact that insulin was, in effect, a 'class remedy'.³⁸ Questions were asked in Parliament, but drew only the response that Poor Law guardians could fund insulin for the destitute;³⁹ however, Poor Law relief was only available to about 1.5 % of the population.⁴⁰ Dr Otto Leyton of the London Hospital wrote:

Personally, I do not treat patients in hospital with insulin unless I am satisfied that they will be able to obtain a supply after leaving. It is too cruel to let an individual learn that there is some substance which will allow him to live in comparative comfort, but because he has not money to buy it he must perish miserably.⁴¹

A general practitioner in Yorkshire described how he treated his poorer patients with 'an amount of insulin per day commensurate with their means', in doses varying between 5 and 20 units daily.²² He concluded that even small doses were of some benefit and that every patient

... should be urged to spend what money he can afford on insulin, resting assured that it will be returned to him a hundred fold in strength, happiness, and increased earning capacity.

The physicians at St Bartholomew's Hospital in London used a small single daily dose of insulin in conjunction with a low calorie diet with severe restriction (16 g daily) of carbohydrate, primarily in the belief that this would help protect the remaining beta cells, but cited the low insulin dose (and therefore lower cost) as an additional advantage.²⁰

It was not until the early 1980s that the policy of using low carbohydrate diets was officially abandoned in the UK and Europe,⁴² and it is of interest that Deckert and his colleagues, who studied patients who had been treated for up to 40 years, found lower mortality rates in those patients who had been treated with 0.31–0.50 units kg⁻¹day⁻¹ than in those who had received more than 0.5 units kg⁻¹day⁻¹.⁴³ Whether this finding was the result of lower carbohydrate diets in those who received lower doses of insulin, or whether it reflects a less 'severe' form of the disease in these patients, is not known, but it does have potential implications in an era

Table 3. Expenditure on Insulin and other drugs in Hereford Hospitals in 1923 and 1997

	Hereford General Hospital 1923	Hereford Hospitals NHS Trust 1997
Beds	100	400
Pharmacy expenditure per week (excl staff) (£)	9.05 ³²	25 120 ³³
Cost of 1 week's treatment (£)		
Insulin 230 units		
Beef (July 1923)	2.01 ³⁰	–
Hypurin Neutral	–	3.88 ³⁴
Lentard MC	–	1.34
Actrapid	–	2.31
Erythropoietin 9000 units	–	80.35
Human growth hormone 36 units	–	274.50

when we are trying to minimize the prevalence of microvascular complications at the expense of greater hyperinsulinaemia with its theoretical consequences for macrovascular disease.⁴⁴

The cost of insulin is still a major problem for many diabetic patients in poorer countries.⁴⁵ Even when insulin is made freely available, food is not, and those on monthly salaries may be affected by an 'end of month hypoglycaemia syndrome' caused by missed meals as money gets short.⁴⁶ A similar problem may have faced those few patients in the UK who received free insulin because they were on Poor Law assistance.³⁹

Effect of Insulin Therapy on the Medical Profession

The introduction of insulin therapy posed new problems of clinical management for which most doctors were completely unprepared. In a lecture to the Brighton and Sussex Medico-Chirurgical Society in October 1923⁴⁷ Dr Sanderson commented that:

... whatever may be the benefit conferred upon the diabetic by insulin, there seemed little doubt that it bade fare to bring many practitioners to a premature grave, so multitudinous, bewildering, and worrying were the problems involved.

Seventy-five years on, some hard-pressed diabetologists may feel that, in this respect at least, nothing much has changed!

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